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IMPLICATIONS TO MAN OF IRRADIATION BY INTERNALLY DEPOSITED STRONTIUM-89, STRONTIUM-90, AND CESIUM-137

Federal Radiation Council
Washington, D. C.

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A report of an Advisory Committee from the Division of Medical Sciences: National Academy of Sciences - National Research Council, Washington, D.C.

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FEDERAL RADIATION COUNCIL
Washington, D.C.

FOREWORD

In its continuing assessment of the health implications of exposure of man to ionizing radiation, the Federal Radiation Council invited the National Academy of Sciences to aid it in reviewing various aspects of the field. An Advisory Committee to the Federal Radiation Council was duly appointed by the Academy within the Division of Medical Sciences of the National Research Council.

The first request of the Federal Radiation Council was for a summary statement concerning the effects to be expected in man from irradiation by internally deposited strontium-89, strontium-90, and cesium-137, with reference to effects that might occur at dose levels of the order of 25 rads or less. The report which follows was prepared by the Advisory Committee. It surveys the possible effects of these nuclides in man in light of their particular metabolic properties and in relation to the known effects of irradiation from other internally deposited radioelements and from external sources.

The views of the committee are based on evidence documented in the scientific literature and reviewed extensively in cited reports by the National Academy of Sciences Committees on the Biological Effects of Atomic Radiation, by the United Nations Scientific Committee on the Effects of Atomic Radiation, and by the Medical Research Council Committee on the Hazards to Man of Nuclear and Allied Radiations. No attempt has been made to discuss the evidence fully again at this time. Consequently, the presented material is submitted as a working paper for the use of the Federal Radiation Council.

Arthur C. Upton, Chairman

Howard L. Andrews
Victor P. Bond
Cyril L. Comar
James F. Crow
Samuel P. Hicks
Brian MacMahon
Joseph E. Rall
W. L. Russell
Eugene L. Saenger
Shields Warren

31 December 1964

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SECTION I

INTRODUCTION

1.1 All ionizing radiations can cause the same types of biological effects, the probability of any given effect depending on the conditions of exposure. Consequently, the hazards of irradiation from radioactive strontium and cesium, as from any internally deposited radionuclide, depend on the distribution of the elements in the body, their retention, and their radioactive decay. These properties, in turn, depend on the chemical behavior of strontium and cesium in the forms in which they are encountered and on the physical characteristics of their several isotopes.

1.2 Cesium-137 is an alkali metal chemically similar to potassium, which it resembles metabolically. As such, it is distributed relatively uniformly throughout the body and is excreted largely within a period of months. Because of the distribution of cesium-137 in the body, the radiation from this isotope resembles whole body irradiation. It is a beta-emitter, decaying with a physical half-life of 29.7 years, to form barium-137m, which in turn decays almost at once with emission of gamma rays.

1.3 Strontium is an alkaline earth, similar to calcium and radium in its metabolism by the body. As such, it has a predilection for bone, into which it becomes tightly bound and from which it is excreted slowly over a period of years. Because the radiation from strontium-89 and strontium-90 is localized primarily in bone and to a lesser extent in bone marrow, the nuclides give rise to exposure principally of these tissues, although they may irradiate other parts of the body in the process of uptake and excretion. Both nuclides are beta-emitters, with physical half-lives of 50.5 days and 27.7 years, respectively. On decay strontium-90 gives rise to a beta-emitting daughter element, yttrium-90, which has a physical half-life of about 2.5 days.

1.4 Principles for evaluating the health implications of radionuclides, as summarized in earlier reports by the Federal Radiation Council (No. 3, 1962; No. 5, 1964), have laid stress on permanent somatic and genetic effects, which may be induced by low-level irradiation in the absence of immediate or obvious manifestations of radiation injury. In the report that follows, these principles will be applied primarily to a consideration of the health implications of the uptake of strontium-89, strontium-90, and cesium-137 by a small fraction of the population on a short-term basis (i.e., for a period of days to months).

1.5 The evaluation of the effects of these nuclides involves many uncertainties and depends heavily on extrapolation from studies with experimental animals, since observations on the effects of radioactive strontium and cesium in man are fragmentary.

1.6 With whole body exposure, such as from radioactive cesium, the possible effects of chief concern are genetic damage, leukemia, and other neoplasms. Other effects to be considered, however, include injury to the developing fetus, life-shortening, and retardation of growth.

1.7 With localized irradiation of the bone and bone marrow, as from radioactive strontium, the principal effects to be considered are induction of bone tumors and leukemia, as well as disturbances in the growth and development of skeletal parts and teeth.

1.8 Although radionuclides of cesium and strontium are considered separately in this report, it is recognized that they will be encountered together in most instances of contamination.

SECTION II

CESIUM

Metabolism

2.1 Cesium exists as stable cesium-133 in mammals in a concentration of about 10^{-4} μgrams per gram of wet tissue. Cesium-137 is the only isotope of cesium that makes an appreciable contribution to the radiation dose to man. Cesium-134 has been detected in man but only in the presence of a much greater activity of the longer lived cesium-137.

2.2 Cesium-137 is a fission product which enters the human food chain primarily by deposition on foliage that is later consumed by domestic animals. The amount of cesium-137 that enters the human food chain appears to increase with the amount of rainfall in the area where dairy cattle graze (Rickard et al., 1962). The major portion of the cesium-137 burden in the United States population comes from the consumtpion of milk and milk products; meat products are the second most important source (Anderson, E. C. et al., 1957). A relatively high cesium-137 burden has been found in Swedish Lapps (Liden, 1962), resulting from the consumption of reindeer meat which, in turn, derived its cesium from a lichen having a high affinity for extracting this element from its environment. A similar food chain appears to account for the relatively high cesium-137 levels found in the Northern Alaskan Eskimos (Hanson et al., 1964). Elevated levels have been reported in other populations living in the far north (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964).

2.3 Cesium-137 has been detected in edible marine organisms, including fish, but the concentration factors are too small to make an important contribution to the total human intake.

2.4 Cesium-137 has also been observed in human milk (Aarkrog, 1962). The cesium-potassium ratios in human milk range up to about twice the corresponding ratios in the mother's diet, indicating that the mammary gland tends to concentrate cesium in the milk relative to potassium. The cesium-potassium ratios in human milk parallel but are slightly higher than the corresponding ratios in cow's milk from neighboring areas. The absolute cesium-137 content per unit volume is lower in human milk than in cow's milk, however, because the latter contains about three times as much potassium as the former.

2.5 Measurements in animals (Moore and Comar, 1963) show that a developing fetus comes rapidly into cesium-137 equilibrium with cesium ingested by the mother. In a small number of observed cases the concentration of cesium in children shortly after birth was essentially the same as that in the mother (Bengtason et al., 1964).

2.6 Most cesium salts are quite soluble and hence are rapidly and completely absorbed, with little dependence upon the route of administration. Tracer studies in the cow show that about 13 percent of a *single* cesium-137 dose appears in the milk over a 30-day period (Hood and Comar, 1953). In a woman essentially in cesium equilibrium,

over 40 percent of the daily cesium-137 intake appeared in the milk at the beginning of lactation, this proportion decreasing to about 20 percent within a few months (Aarkrog, 1962).

2.7 Cesium, like potassium, tends to be found within cells, although small extracellular concentrations are observed. Assays of Japanese autopsy specimens (Yamagata, 1962) produced the values in Table 1.

Table 1. Cesium-137 concentration in Tissues of Japanese People*

Tissues	pCi of ^{137}Cs per gm of tissue	pCi of ^{137}Cs per gm of K
Muscle	29.5	13.2
Soft tissues	12.7	9.8
Bone and marrow	15.7	9.1
Average all tissues	20.0	10.0

*From Yamagata, 1962.

2.8 Although the distribution of cesium is somewhat different from that of potassium, over 55 percent of the cesium-137 burden can be expected to be in the total muscle mass.

2.9 The retention of ingested cesium as a function of time is a most important factor in any estimate of absorbed dose. Although some data have suggested that there is little choice between an exponential function and a power law function, retention studies which have been extended over several hundred days favor a two-component exponential function (Stewart et al., 1958; United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). The short lived component with a biological half life of the order of one day contributes little to the total absorbed dose and can be neglected.

2.10 Biological half life values for the long lived component range from about 74 days (Liden, 1962) to 180 days (Stewart et al., 1958) in adults, with lower values for children (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). The range of observed values appears to represent differences among individuals rather than instrument or calibration errors. Values obtained by whole body counting agree well with those obtained by assays of excreta. A similar two-component exponential retention function was found in the dog (Nold et al., 1962), with biological half lives in a small series ranging from 18.8 to 40.9 days.

2.11 Data from adults are too meager as yet to permit a precise determination of a most probable biological half life, and indeed this value may be a function of the eating habits of a population. Retention data in children are even more meager, and few children have been studied for the lengths of time required to obtain good values of biological half life. During the first decade after birth, biological half lives for cesium-137 may be less than one-third of the adult value.

2.12 In the light of these uncertainties, a value of 100 days has been taken as the biological half life of cesium-137 in normal adults of the general population (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). This value is almost certainly too large for children, perhaps by a factor of three to five. The use of too large a value of the biological half life will lead to an overestimate of the absorbed radiation dose.

2.13 Exposure to cesium-137 from weapons fallout is more apt to be long-continued, at an approximately constant level, than is exposure that might result from an industrial accident, which is apt to be limited to a single, brief period.

2.14 To illustrate the build-up of a cesium body burden, let us consider a steady-state situation in which there is a constant daily intake of k nanocuries of cesium-137. If a biological half life of 100 days is assumed, the effective decay constant $\lambda = 0.693/100 = 6.93 \times 10^{-3}$/day. At any time t days after the start of exposure, the body burden B in nanocuries will be given by

$$B = \frac{k}{\lambda}(1 - e^{-\lambda t}) \qquad \text{E–1}$$

$$= 144\,k(1 - e^{-0.00693t}) \qquad \text{E–2}$$

There will be a maximum body burden at equilibrium of

$$B_M = 144k \qquad \text{E–3}$$

but this value will be approached slowly. B will reach 90 percent of its maximum value in about 330 days.

Dosimetry

2.15 In calculating the absorbed dose, it seems reasonable to assume that the body burden is uniformly distributed throughout the body. The variations in concentration between one tissue and another are smaller than the uncertainties in the half-time of retention for a given individual. The tissue dose will come mainly from the beta particles emitted by cesium-137 itself and from the gamma rays emitted by its metastable daughter barium-137m (ICRP, 1960). The range of most of the beta particles will extend well beyond cellular boundaries, so that extracellular tissues will receive a radiation dose comparable to that delivered to the interior of the cell.

SECTION III

STRONTIUM-89 AND STRONTIUM-90

Metabolism

3.1 The behavior of strontium in mammals is inextricably linked with that of other elements, especially calcium. It is also affected by variations in nutrition, bone physiology, fetal development, and lactation. It is not feasible in this report to attempt a rigorous consideration of all such factors in estimating the hazard from radiostrontium to man; instead, attention is given primarily to conditions that would result from short-term contamination, in which case it is assumed that fresh cow's milk would be the principal contributor to the body burden.

3.2 The metabolic properties described below are equally valid for strontium-89 and strontium-90. In this discussion, radioactive strontium is designated as Sr*.

3.3 After radiostrontium is ingested, part of it is absorbed from the gastrointestinal tract into the blood stream and part is excreted unabsorbed in the feces. That which is absorbed is (a) deposited in the skeleton, (b) distributed in the soft tissues and circulating fluids, or (c) removed from the body by urinary excretion and endogenous fecal excretion (United Nations Scientific Committee on the Effect of Atomic Radiation, 1962, 1964; Comar and Wasserman, 1964; Loutit, 1962; Caldecott and Snyder, 1960).

3.4 The pattern of skeletal distribution after short-term exposure can be pictured as follows: Radiostrontium from the blood rapidly enters the bone by ion exchange on the surfaces of bone crystal and by incorporation into new bone which is being formed in zones of growth and remodeling. This leads to focal areas of highly localized radioactivity and diffuse areas of generally lower concentration. In young, growing individuals and in cancellous bone formation rates are relatively high, resulting in comparatively high local deposition and intensity of radioactivity.

3.5 The removal of radiostrontium from bone, once it has been deposited, is relatively slow, depending mainly upon the extent of bone resorption and mineral exchange.

3.6 The behavior of strontium in the body can be considered either in terms of strontium itself or in terms of the relation between strontium and calcium (United Nations Scientific Committee on the Effects of Atomic Radiation, 1962; Comar and Wasserman, 1964; Caldecott and Snyder, 1960; Wasserman, 1963). Although the data on the retention of strontium in the body suffice for estimating body burdens for short-term ingestion, analysis of the strontium-calcium relationship facilitates estimating concentrations of radiostrontium in newly formed bone and in the entire skeleton under conditions of protracted intake. The reasons for this are (a) homeostatic control of calcium leads to a remarkable constancy of calcium concentrations in most tissues and fluids; (b) strontium metabolism is regulated more by calcium levels than by normal amounts of stable strontium; and (c) strontium and calcium movements are usually affected similarly by extraneous factors. Extensive experimental evidence in man and animals shows that the strontium-to-calcium

ratio in tissues and secretions is directly related to the ratio that exists in the diet, within normal dietary limits.

3.7 Organisms generally utilize and retain strontium less effectively than calcium; that is, they *discriminate* against strontium in favor of calcium. The term "Strontium-Calcium Observed Ratio" (OR) is used to denote the comparative strontium to calcium ratios that exist at equilibrium in a given component of the body and in its dietary precursor; for example,

$$OR_{bone/diet} = \frac{\text{Sr/Ca of bone}}{\text{Sr/Ca of diet}} \qquad \text{E–4}$$

3.8 The over-all discrimination, which is designated by the OR value, is brought about by one or more physiological processes, of which gastrointestinal absorption, renal excretion, placental transfer, and mammary secretion are most important (Comar and Wasserman, 1964).

3.9 The OR value is affected by age and dietary composition, although the effects of the latter are small unless the diet is highly exceptional. Under the usual dietary conditions the OR values for older children and adults fall within a reasonably narrow range, with few indications of variation by a factor as high as two (United Nations Scientific Committee on the Effects of Atomic Radiation, 1962; Comar and Wasserman, 1964).

3.10 In the movement of strontium and calcium between bone and the exchangeable pools there is little or no discrimination between the two elements. The terms $OR_{body/diet}$ and $OR_{bone/diet}$ are, therefore, used interchangeably. If the skeleton of an individual is formed entirely from a diet of a given Sr*/Ca ratio, then all the bone should have an essentially uniform concentration, equivalent to $(OR_{bone/diet}) \times$ (Sr*/Ca of diet); an example of this would be the case of a newborn child of a mother who had a constant dietary Sr*/Ca during gestation.

3.11 Under conditions of short-term exposure to radiostrontium or exposure to changing levels the situation is much more complex. The highest concentrations are localized in "hotspots" which represent sites of active bone formation and are estimated to contain about half of the deposited radiostrontium. The rest of the radioactivity is diffusely distributed in bone at a considerably lower concentration than in the "hotspots" (La Croix and Budy, 1962). The theoretical maximum concentration is equal to the value of $(OR_{bone/diet}) \times$ (Sr*/Ca of diet). In actuality, it is expected that the concentration in "hotspots" may be as low as half the theoretical maximum because of the contribution of calcium from the body stores.

3.12 Also significantly influencing the deposition and retention of radiostrontium is the rate of turnover of bone salts, or the rate of replacement of existing mineral in the skeleton. Some considerations suggest that the skeletal calcium of the newborn infant turns over so rapidly that appreciable equilibration of skeletal strontium to calcium ratio with the strontium to calcium ratio of the circulating fluids probably occurs within a matter of weeks (Comar et al., in preparation). This means that the strontium to calcium ratio of the skele-

tion of the newborn infant will be governed primarily by the strontium to calcium ratio of the diet during the first few weeks, and perhaps months, after birth. In infants and young children it has been estimated that about 50 percent of bone mineral is replaced annually, with an almost complete replacement of skeletal mineral in the first two years of life (Bryant and Loutit, 1964). In older individuals, a gradation of replacement rates is thought to exist; for example, it is estimated that the replacement rate in adult long bones might be about 1 percent per year as compared to about 10 percent in adult cancellous bones (Loutit, 1962). Those parts of bone with the highest growth-rate are those in which are deposited the largest amounts of the radiostrontium ingested over a short time period.

3.13 Typical data for estimation of body concentrations of radiostrontium following short-term contamination of cow's milk are summarized in Table 2. The values have been appropriately rounded, since no single figure can be representative of an entire population, and since the values are intended only for illustrative comparisons and rough estimates.

3.14 The values for $OR_{body/diet}$ (column 1, Table 2) are as follows: for the fetus, a rounded value of 0.1 was used, although the data in the literature would suggest values up to 0.13 (United Nations Scientific Committee on the Effects of Atomic Radiation, 1962; Comar and Wasserman, 1964; Loutit, 1962); the OR value at birth is close to 1 (Lough et al., 1963), decreasing to about 0.5 at 1 year of age and probably reaching the adult value of 0.25 sometime shortly thereafter (United Nations Scientific Committee on the Effects of Atomic Radiation, 1962; Loutit, 1962; Benison et al., 1964); for pregnant and nursing women, the value accepted for adults (0.25) was used.

3.15 The fraction of the calcium intake that might be derived from fresh cow's milk was calculated from consideration of the amount of calcium consumed in fresh milk (column 3, Table 2) in relation to the total calcium intake (column 2, Table 2). The data on column 2, Table 2, were derived from recommended dietary intakes (Food and Nutrition Board, 1958 and 1963) and in column 3, Table 2, from estimates of milk consumption in home and school (Bureau of the Census and Division of Radiological Health, 1963). The diet of babies less than 4 months of age will contain no fresh cow's milk if they are breast-fed or receive formulas made with processed milk; however, for purposes of comparison, an entry has been made for such infants fed a diet based entirely on fresh cow's milk.

3.16 The values in column 5, Table 2, which represent the maximum Sr*/Ca in new bone per unit of Sr*/Ca in cow's milk, were calculated by multiplication of columns 1 and 4. The highest concentrations occur in the 4–6 month age group (except for the 0–4 month infant fed on fresh cow's milk) and are 2 to 5 times higher than those calculated for ages 6 months to about 20 years.

3.17 The daily retention of Sr* per unit of Sr*/gram of calcium in fresh milk (column 6, Table 2) was calculated on the basis of a gastrointestinal absorption of 30 percent (Lough et al., 1963; Gran and Nicolaysen, 1964), neglecting endogenous losses, which are small. These values do not apply to long-term ingestion, since under chronic

Table 2

Estimation of Body Concentration of Radiostrontium Resulting from Short-term Ingestion of Contaminated Fresh Cow's Milk

Age, Nutrition, and Physiological Status	(1) $OR_{body/diet}$	(2) Calcium intake g/day	(3) Calcium intake from fresh cow's milk [a] g/day	(4) Fraction of calcium intake from fresh cow's milk	(5) Maximum Sr*/Ca in new bone per unit of Sr*/Ca in cow's milk	(6) Daily Sr* retention per unit of Sr*/g of Ca in fresh milk [b]	(7) Calcium content of Body (g)	(8) Daily Sr* retention per gram of Ca in body per unit of Sr*/g of Ca in fresh milk
Fetus	0.1	—	—	—	0.07	—	—	—
0–4 mo. (breast-fed)	1.0	—	—	—	0.06	—	—	—
0–4 mo. (processed milk)	1.0	—	0	0	0	—	—	—
0–4 mo. (fresh cow's milk)	1.0	—	—	1.0	1.0	—	—	—
4–6 mo.	1.0	1.0	0.8	0.8	0.80	0.24	52–64	0.0041
6 mo.–1 yr.	0.5	1.0	0.8	0.8	0.40	0.24	64–100	0.0029
1–4 yr.	0.25	1.0	0.6	0.6	0.15	0.18	100–201	0.0012
4–9	0.25	1.0	0.8	0.8	0.20	0.24	201–341	0.00089
9–14	0.25	1.2	0.8	0.7	0.18	0.24	341–715	0.00045
14–19	0.25	1.4	0.8	0.6	0.15	0.24	715–1073	0.00027
19–24	0.25	0.8	0.4	0.5	0.13	0.12	1073–1078	0.00011
24	0.25	0.8	0.3	0.4	0.10	0.09	1078	0.00008
Pregnant Women	0.25	1.5	1.1	0.7	0.18	0.33	1078	0.00031
Nursing Women	0.25	2.0	1.1	0.6	0.15	0.33	1078	0.00031

[a] These values also represent the daily Sr* intake per unit of Sr*/gram of calcium in fresh cow's milk.

[b] Based on 30% gastrointestinal absorption.

conditions the skeleton tends to approach a steady state with regard to Sr* entry and removal, and the excretion from the body increases. From estimates of the total calcium of the body (Mitchell et al., 1945), the daily retention of Sr* per unit of Sr*/gram of calcium in fresh milk can be expressed in relation to the amount of calcium in the body (column 8, Table 2). For example, an adult man is estimated to consume daily 0.3 gm of calcium from fresh cow's milk; if this milk contained 1 picocurie of Sr*/gm Ca, it is assumed that he would consume 0.3 picocurie of Sr* of which 30 percent, or 0.09 picocurie, would be retained. If his body content of calcium were 1078 gm, then his daily retention of Sr* per gram of calcium in his body would be about 0.00008 picocurie.

3.18 The rate of elimination of radioactive strontium from the body, as influenced by age and other factors, is not well-known. Studies in several species of laboratory animals have indicated that the rate of excretion of strontium-85 varies markedly in relation to age during the first few months after a single injection of the isotope but later approximates the same power function in animals of all ages (see Finkel, Bergstrand, and Graubard, 1960; Speckman and Norris, 1964; Decker et al., 1964). Limited human data fitted with a power function and extrapolated to 40 years give a long-term retention half life of 110 years, or 4.0×10^4 days (Cohn et al., 1962), as compared with the half life of 1.3×10^4 days listed by the ICRP (1960). The difference between the two half lives is attributable in part to a relatively rapid rate of excretion during the first several months, which can be described by three successive exponential functions with half lives of 2.5, 13.7, and 843 days, respectively (Cohn et al., 1962). Clearly, more data are needed over longer intervals to enable confident prediction of the long-term retention of radioactive strontium by human populations of various ages following short-term intake.

3.19 Although the initial concentrations of radiostrontium are obviously highest in young infants fed fresh cow's milk, the turnover of the isotope and its removal from the body are also relatively high in infancy. Because these opposing effects cannot yet be balanced precisely, it is difficult to state unequivocally which age group of the population may receive the largest cumulative radiation dose from short-term ingestion of strontium-90. Strontium-89, however, which has a physical half life of only 50.5 days, will tend to be removed more slowly by excretion at all ages than by radioactive decay, so that the cumulative radiation dose from this isotope will depend primarily on its initial concentration in the body.

Dosimetry

3.20 It is not yet possible to interpret the radioactive strontium burden meaningfully in terms of the relevant resulting radiation dose to the target tissue of interest, especially under conditions of relatively short-term exposure to strontium-89 or strontium-90. At any given time, the maximum local concentration of radioactivity in the skeleton, and thus the maximum dose in "hotspots", depends on the Sr*/Ca in new bone (column 5, Table 2). On the other hand, the average concentration of radioactivity in the skeleton, and thus the average dose to bone, is related to the ratio of Sr* in the body to the total calcium in the body. Use can be made of either of these values to estimate the corresponding doses in

rads (see Loevinger, 1956; Mays et al., 1959; ICRP, 1960; United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). The difference between the resulting two doses is large, and which of the two, if either, is appropriate in estimating health hazards is not clear. In general, however, values of the mean dose to bone are used, although it is recognized that they would be strictly appropriate only if the incidence of the effects in question varied as a linear function of the dose to bone over a wide range of doses. When the absorbed dose to the bone from these nuclides is used in this report, it will refer to the mean dose in rads.

SECTION IV

GENETIC EFFECTS

4.1 Appraisal of genetic injury is hampered by our inability to measure the over-all damage resulting to the population from the total effects of deleterious mutations. Nevertheless, it is accepted that any increase in the mutation rate is undesirable, since mutations are preponderantly harmful and are transmittted to successive generations. Furthermore, since any increase in the radiation dose to germ cells is assumed to cause some increase in the mutation rate, the National Academy of Sciences-National Research Council Committee on Genetic Effects of Atomic Radiation recommended in 1956:

> "That for the present it be accepted as a uniform national standard that X-ray installations (medical and nonmedical), power installations, disposal of radioactive wastes, experimental installations, testing of weapons, and all other humanly controllable sources of radiations be so restricted that members of our general population shall not receive from such sources an average of more than 10 roentgens, in addition to background, of ionizing radiation as a total accumulated dose to the reproductive cells from conception to age 30.
>
> That individual persons not receive more than a total accumulated dose to the reproductive cells of 50 roentgens up to age 30 years (by which age, on the average, over half of their children will have been born), and not more than 50 roentgens additional up to age 40 (by which time about nine tenths of their children will have been born)."

4.2 The 1956 report was written before it was demonstrated in mice that, for those germ cell stages which, in man, are the ones of primary concern, an exposure to low-dose-rate radiation is less mutagenic than the same total dose given at a high dose rate. At about the same time, the susceptibility of human chromosomes in somatic cell cultures to breakage by radiation doses as low as 25 R was reported. After weighing the various aspects of these and other new developments, the Committee reiterated its position in 1960, reporting as follows:

> "The Committee continues to recommend that for the general population the average gonadal dose accumulated during the first 30 years of life should not exceed 10 r of man-made radiation, and should be kept as far below this as is practicable. This is in essential agreement with the most recent suggestions of the International Commission on Radiological Protection."

4.3 The Committee did not comment further at this time with reference to the individual dose.

4.4 The last decade has been one of significant progress in genetics and molecular biology. Many of the details by which the DNA molecule replicates, mutates, carries information, and influences development are now known. The basic principles of protein synthesis under the control of DNA through the mediation of RNA are beginning to be

understood. The identification of DNA with the gene has made possible a rational study of chemical mutation, and a number of compounds known to affect DNA in one way or another have been shown to alter the mutation rate. There has also been considerable progress in understanding some of the chemical steps in the induction of mutation by ultraviolet radiation. The induction of mutation by ionizing radiation is less understood at the chemical level, but the biological knowledge of such mutation has been greatly increased. For example, the mutation process has been found to be dependent on a great many variables in a complex way. The stage of the cell in mitosis, the stage in the life cycle, the amount of oxygen in the cell, and a number of other factors have all been shown to be influential. There is also strong evidence for cell selection that can diminish, or perhaps in some circumstances increase, the impact of a mutation. When the 1956 report was written some of this was realized, but the problem of estimating the damage from radiation seemed simpler in some ways than it does now. In particular, at that time it was not realized that the dose rate was of importance. The roles of this and other factors, including complexities in the different mutational responses of male and female germ cells, have now been revealed through intensive studies in mice (Russell, 1963).

4.5 The science of human cytogenetics has been advanced considerably since the 1956 report. It is now realized that several types of human abnormality—severe syndromes with various physical defects and mental retardation—are caused by chromosomal aberrations. It is well established in experimental animals that nondisjunction, chromosome loss, and translocation are increased by radiation. Furthermore, it is now possible to study chromosome breakage and rearrangement in humans in the same manner as has been so productive of new information in plant genetics. Recent reports emphasize that irradiation in vitro with doses down to about 12 R causes about 1 percent of human somatic cells to have chromosome abnormalities, and radiation workers receiving approximately 10 times the background dose have been demonstrated to have a significant increase in abnormal chromosomes in circulating white blood cells (Norman et al., 1964).

4.6 There have been almost no reports on the mutagenic effects of radioactive strontium and radioactive cesium. Embryo mice from fathers that had received intravenous injections of 0.7 microcurie of strontium-90 per gram of body weight have been reported to have a higher frequency of cells with an abnormal number of chromosomes than the controls (Henricson and Nilsson, 1964). The authors stated that the results could be due to radiation-induced aneuploidy in the germ cells, but suggested that another type of damage not primarily connected with the chromosomes may have been involved; namely, a radiation effect on the cell division mechanism that was transferred from spermatozoa to embryos. The same large amounts of strontium-90 injected intraperitoneally in mice have been reported to produce a significantly higher embryonic mortality in descendants than was found in the controls or after injection of the same number of microcuries of cesium-137 (Lüning et al., 1963a, 1963b). The effect was interpreted by the authors as resulting from incorporation of strontium-90 in the chromosomes. This interpretation raises the question of whether radioactive strontium should be given special consideration as a genetic factor. However, as the authors pointed out, there are apparently some puzzling inconsis-

tencies in the results which cannot be resolved without further experiments. Furthermore, even if the magnitude of the reported effect were confirmed, it woud still seem unlikely that it would prove to be the limiting factor in setting up protective action guides for strontium-90. In the first place, the doses to the mice were large (about 18 microcuries per mouse). Second, the length of time the strontium stays in the germ cells, or even in their vicinity, is probably only of the order of days, and most of it that is not deposited in the bones is excreted.

4.7 A number of large-scale population studies on mammals have been completed or are under way (see Roderick, 1964). In general, doses delivered to mature germ cells at high dose rates have been observed to cause detectable effects on viability, size, and similar traits in the first generation progeny. Thus, large doses given to rats have been shown to have a significant effect on the maze-learning ability of their progeny (Newcombe and McGregor, 1964). Also, a significant increase in skeletal abnormalities has been found in the offspring of irradiated mice (Ehling and Randolph, 1962; Ehling, 1964). But experiments that have utilized radiation to premeiotic germ cells have, in general, been inconclusive, even when several generations have been examined. The inconclusive nature of the experiments should not be regarded as evidence against the existence of radiation-induced effects, but rather as an indication of the difficulty of precise study of such effects. Consistent with this thesis is the absence thus far of conclusive evidence of any substantial increase in overt genetic effects in the offspring of the Japanese A-bomb survivors (United Nations Scientific Committee on the Effects of Atomic Radiation, 1962).

4.8 Quantitative assessments of the genetic risk to human beings from radiation exposure are difficult because of the fact that almost all the information comes from experimental animals. The problems of differential cell sensitivity, dose-rate effects, inter-cell selection, and the other complications all make it very difficult to assess the full impact of radiation even on a mouse population. In man the problem is compounded by the fact that the social impact of mutation depends on a number of uniquely human factors. The variety of effects that can occur as a result of mutation and chromosomal anomaly, and the incidence of these, have been discussed repeatedly (National Academy of Sciences-National Research Council, 1956, 1960; Medical Research Council, 1956, 1960; United Nations Scientific Committee on the Effects of Atomic Radiation, 1962; Federal Radiation Council, May, 1962).

4.9 In choosing the 10 R limit for population 30-year exposure, the Genetics Committee thought, for a variety of reasons, that doses below this level, although not desirable, would be acceptable if there were compensating benefits. It was also thought that the chance of genetic damage of such a nature as to affect the individual (by being expressed in his immediate family) would be acceptably small if the individual dose were kept below 50 R. The reasons for this conclusion still seem to be valid.

4.10 In reference to the dose of 25 rads of interest in this report, it may be noted that this is below the level that the Genetics Committee set for an individual dose, and

would presumably be received at dose rates lower than those which had to be considered by that Committee. Furthermore, as long as the group exposed is small, the average dose to the population will not be greatly changed. Therefore, genetic considerations are not likely to be limiting if the exposed group constitutes a small fraction of the population.

SECTION V

SOMATIC EFFECTS

Effects on Embryological Development

5.1 A single, brief exposure of the mammalian fetus to as little as 10 or 20 R of X-rays has been noted to cause abnormalities of brain development carrying over into adult life (Hicks and D'Amato, 1963). Developmental skeletal abnormalities have been increased in mice genetically disposed to show them following a single, brief X-ray exposure at even the lowest dose level tested, namely 25 R (Russell, 1957).

5.2 Protracted exposure of mice, on the other hand, to a continuous dose of 12 R a day throughout the first 15 days of pregnancy has been observed to produce no gross anatomical abnormalities in the exposed offspring, although it shortened the reproductive life of the exposed female young (Russell et al., 1960). Exposure of pregnant rats to 1 R a day for 20 days has been reported to cause detectable changes in the development of behavior in the exposed offspring (Piontkovsky and Semagin, 1961; Piontkovsky, 1961); i.e., retarded development of conditioned reflexes and poorly retained reflexes. The brains of the affected offspring were said to be smaller than normal.

5.3 Effects of strontium-89 on development have been observed in one study with mice (Finkel, 1947). The doses injected were relatively high, 1 to 10 microcuries per gram weight in the pregnant animal. Strontium-89 was deposited in the bones of the offspring. The higher doses of strontium-89 resulted in stillbirth. At lower doses of strontium-89, retarded growth, malformation of the skeleton, anemia, and osteogenic sarcoma were noted.

5.4 Malformations have been increased in frequency in the human embryo and fetus by relatively large doses of radiation delivered at high dose rates. For example, an abnormally high incidence of microcephaly with mental retardation has been noted among Japanese children exposed in utero to the atomic bomb (see Burrow et al., 1964). From the meager data available, however, it is not possible to determine the relationship between the risk of severity of such effects and the radiation dose.

5.5 On the basis of a small study, it has been suggested that heterochromia of the iris may be related to prenatal diagnostic X-ray exposure (Lejeune et al., 1960), but in a subsequent, much larger study, the suggestion was not confirmed (Cheeseman et al., 1963). At the present time it seems unlikely that there is a causal association between prenatal X-ray exposure and heterochromia iridia, although the possibility of a much lower order of association than that originally reported cannot be unequivocally excluded.

Prenatal X-ray Exposure and Childhood Cancer

5.6 An association between prenatal X-ray exposure and the incidence of cancer in childhood has been reported, which is important in the present context because of the relatively small dose of radiation involved.

5.7 The original observation (Stewart et al., 1956; Stewart et al., 1958) was that about twice as many mothers of children who died of cancer reported diagnostic X-ray examination during the relevant pregnancy as did mothers of normal children. The significance of the finding was widely questioned because of the investigators' reliance on mothers' recall of X-ray exposures that may have occurred up to 10 years before. However, a number of subsequent studies, utilizing different methods, have confirmed the observation, although at a somewhat lower level of association than the original study (Ager et al., 1962; Ford et al., 1959; Kaplan, 1958; MacMahon, 1962; Polhemus and Koch, 1959). Some negative studies have been reported (Court-Brown et al., 1960; Kjeldsberg, 1957; Lewis, 1960; Murray et al., 1959; Wells and Steer, 1961), but all are based on small numbers of cases and no published study reports results significantly different (statistically speaking) from the mean value quoted below.

5.8 No factor which might increase both X-ray exposure and cancer rates and thus produce a spurious association has been definitely implicated, although most of the obvious possibilities have been explored.

5.9 If the association is assumed to be one of cause and effect, the maximum likelihood estimate of the cancer risk associated with prenatal X-ray exposure can be calculated. Such an estimate, based on pooled data from all published series (MacMahon and Hutchison, 1964), calculated the cancer risk of the exposed to be 40 percent higher than that of non-exposed children, the 5 percent confidence limits of this figure being 20 and 60 percent.

5.10 The X-ray dose involved in these exposures is not known precisely. For comparable procedures in Great Britain in 1957-58, the Adrian Committee reported a mean dose of 0.8 R to the maternal gonad, but with a range among hospitals from 0.03 to 10 R. It is likely that mean doses in the earlier periods included in the cancer studies were larger—perhaps between 2 and 5 R. The fetal exposure is essentially to the whole body.

5.11 An assumption of linearity in the dose-response relationship at a value of 2 leukemias per million exposed per year per rad, commonly quoted for the relationship in adults, would underestimate the frequency of leukemias associated with fetal irradiation by a factor of between 2 and 5. Associated with fetal irradiation, there are, in addition, other types of cancer (tumors of brain, kidney, and other sites) which have not so far been linked to radiation exposure in adults. In all, between 4 and 10 times as many cancer cases (leukemia and other cancers) are associated with this type of antenatal exposure as would be postulated by assuming an incidence of 2 cases (leukemia only) per million per year per estimated rad.

5.12 These data relate to what is essentially a single exposure—the effect of fractionation is unknown. Also equivocal is the effect of duration of gestation at exposure, the great majority of these procedures being conducted in the last trimester of pregnancy. One large study (Stewart et al., 1958) suggested higher risks for children exposed early in pregnancy, but the finding has not yet been confirmed by other work (MacMahon, 1962).

Effects of Postnatal Exposure

Induction of Leukemia

5.13 An increased incidence of leukemia, a relatively rare disease in man, has been found in various population groups exposed to external radiation in childhood or adult life, as well as in utero. Data on animals given bone-seeking radionuclides indicate that malignancies of hemopoietic tissues may result from internal, as well as external, radiation exposure.

5.14 The incidence of leukemia in man has been observed to be increased after a single dose of external radiation to the whole body at a level of approximately 100 rads or more (Folley et al., 1952; United Nations Scientific Committee on the Effects of Atomic Radiation, 1964) and after irradiation of an appreciable portion of the bone marrow with approximately 500 rads or more (Court-Brown and Doll, 1959).

5.15 In the Hiroshima A-bomb survivors, the incidence of leukemia increased progressively to a maximum between the 4th and 7th years after exposure and declined thereafter, but it was still significantly above the control level in 1960. The incidence of leukemia integrated over the first 15 years after irradiation increased with dose at dose levels greater than approximately 100 rads. Although the exact relationship between dose and incidence has not been established, the increase above the natural incidence averaged over the 15-year period can be calculated to be about 1 to 2 cases per million persons per rad for each year at risk after exposure to 100-500 rads or more. It is not know how long the annual incidence will continue to exceed normal.

5.16 The risk estimate given above cannot be applied to the population at large without reservation. The survivors in Japan were heavily selected as a result of the early lethal effects of the exposure; thus the irradiated survivors may not represent the entire population with respect to susceptibility to leukemia induction. In addition, the increase in incidence more nearly approximated a constant multiple of the natural age-dependent incidence than a constant number of excess cases. Hence, the estimate is probably too high in adolescent children and may be too low in adults; additional data will be needed for accurate estimation in limited age groups.

5.17 External radiation delivered at low dose rates to the entire body or to a large segment of the bone marrow has also appeared to be leukemogenic to human populations at high dose levels (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). Nevertheless, uncertainties about the influence of dose rate, fractionation, and total dose under these conditions make it impossible at present to estimate quantitatively the probability of leukemia under circumstances other than short-term exposure to high doses. Long-term exposure is less leukemogenic than short-term exposure for the same total dose if the dose-rate dependency observed in animals (Mole, 1962; Upton, 1964) also exists in man.

5.18 The types of leukemia showing a relationship to radiation exposure are the acute forms and the chronic granulocytic form (Moloney, 1959; United Nations Scientific

Committee on the Effects of Atomic Radiation, 1964). Related diseases also reported to occur more often than normal in irradiated populations include multiple myeloma (Lewis, 1964; Anderson and Ishida, 1964), aplastic anemia (Lewis, 1964), myelofibrosis with myeloid metaplasia (Anderson et al., 1964), Hodgkin's disease (Anderson and Ishida, 1964), and lymphosarcoma (Anderson and Ishida, 1964). The commonest form of chronic leukemia in the United States and the United Kingdom is the lymphocytic form, the incidence of which has increased during recent years; however, no correlation has been observed between previous radiation exposure and the frequency of this disease.

5.19 The induction of leukemia and lymphomas in animals by external radiation has been amply documented, but the dose-response relation is not precisely known, and there is no conclusive evidence that the frequency of these diseases is increased by less than 50 rads (United Nations Scientific Committee on the Effects of Atomic Radiation, 1962).

5.20 It is reasonably well established that iodine-131 administered in doses greater than 1 curie (e.g., for therapy of carcinoma of the thyroid) may be leukemogenic to man (Moloney, 1959; United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). Hemopoietic tissue receives a considerable radiation dose in the course of such therapy; i.e., of the order of 1.0 rad per millicurie (Sinclair, 1957; Halnan and Pochin, 1958).

5.21 It has not been established whether internal emitters selectively deposited in bone (bone-seekers) are leukemogenic in man. The apparent increase in leukemia among patients with polycythemia vera (Osgood, 1964) treated with phosphorus-32 is suggestive of this but not conclusive in the absence of an adequate control population. Leukemia has been reported in dial painters and other individuals who received radium internally some years previously. Hasterlik et al. (1964) have reported two cases (death certificates) of acute myelocytic leukemia in approximately 400 radium patients, one of which was confirmed by their study of the original blood smear made shortly before the patient's death in 1931. An additional case of myelocytic leukemia has been reported from a series of 150 radium patients studied in New Jersey; the body burden of radium-226 was less than 0.0042 microcurie. No leukemia has been found in a series of 237 individuals exposed to radium studied by Evans and colleagues in Boston.

5.22 Although the human data in themselves are not sufficient to establish that exposure to radium or other bone-seeking isotopes will lead to an increased leukemia incidence in man, large amounts of strontium-90 have been reported to cause leukemia in mice (Watanabe, 1957; United Nations Scientific Committee on the Effects of Atomic Radiation, 1962) and other animals. Furthermore, the onset of leukemias and lymphomas in mice has been found to be hastened with a dose of strontium-90 (8.9 microcuries per kilogram) which did not detectably induce bone tumors or shorten the life span (Finkel, 1959).

5.23 Preliminary results from experiments with dogs and swine (Andersen and Goldman, 1962; McClellan and Bustad, 1964; Andersen and McKelvie, 1964; Biskis et al., 1964) suggest that strontium-90 may induce leukemia and possibly other neoplasms of re-

ticular tissues in these species also, but the data are too limited as yet to disclose dose-effect relationships. The lowest average dose at which such an effect has been observed thus far has been estimated to be 900 rads, delivered throughout life to the skeleton of a dog by strontium-90 administered daily in the diet. The animal in question died at 192 days of age, after being fed since birth a ration containing strontium-90 and after receiving strontium-90 in utero from its dam, which was fed the same ration (Andersen and Goldman, 1962).

5.24 The development of leukemia in 6 chronically strontium-90 treated dogs having cumulative mean skeletal doses of 900-4000 rads and in 3 chronically strontium-90 treated swine having cumulative mean skeletal doses of 16,000-18,500 rads contrasts with the absence thus far of bone tumors at these levels and the absence of leukemias at higher dose levels, where instead bone tumors were induced in high incidence (McClellan and Bustad, 1964; Andersen and Goldman, 1962; Andersen and McKelvie, 1964; Biskis et al., 1964). This dose and dose rate-dependent difference in the types of neoplasms cannot be explained. It may, however, be related to differences in (1) radiation dose rate, (2) radiation dose distribution, (3) age at exposure, (4) latent period of leukemias as opposed to bone tumors, or (5) other factors. Although the apparent differences may not be real, they imply that animals exposed chronically to strontium-90 from infancy may develop leukemia at dose levels lower than those causing a comparable increase in the incidence of bone neoplasms.

Induction of Bone Tumors

5.25 Therapeutic external irradiation has been followed in several dozen human patients by development of osteogenic sarcoma, the neoplasm in most cases arising at the site of a pre-existing benign tumor or chronic inflammation (Bloch, 1962). The latent period preceding the appearance of sarcomas has ranged from less than 3 to over 30 years (Bloch, 1962). In some instances, gross radiation damage to the bone was evident before the neoplasm appeared, but in other instances this was not detected. The relation between the incidence of sarcomas and the radiation dose cannot be inferred from the information at hand, but 3000 rads is the lowest dose thus far associated with the formation of such a tumor in the absence of factors known to predispose to neoplasia (Jones, 1953).

5.26 Doses of external radiation down to 250 R have been reported to induce osteogenic sarcomas in laboratory animals (Koletsky and Gustafson, 1955; Binhammer et al., 1957; Cater et al., 1959; Finkel et al., 1964a, 1964b); however, the natural frequency of such tumors is higher in these animals than in man, suggesting that their susceptibility to radiation neoplasia may also be higher. Precise information on dose-response relationships is not available for any species.

5.27 An increase incidence of benign bone tumors (i.e., osteochondromas) has been noted in children irradiated over the chest with doses ranging from 60-600 R (Pifer et al., 1963). The few tumors observed do not indicate the quantitative relationship between incidence and dose (Toyooka et al., 1963) but they suggest that susceptibility to these effects may be higher in children than in adults.

5.28 The induction of bone tumors in man by internally deposited radionuclides is documented by an increase in the incidence of osteosarcomas with increasing content of radium in the skeleton (Marinelli, 1958; Hasterlik et al., 1964). The available data imply that the tumor incidence more nearly approximates a sigmoid than a linear function of the terminal radium burden (Marinelli, 1958), in keeping with comparable data from experimental mice (Finkel, 1956), but the data are too scanty to define precisely the dose-respone relation. There is no evidence that that the induction of malignancy is associated with a terminal body burden of less than 0.4 microcurie of radium (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). Analysis of the human data is complicated by the fact that measurements of the terminal body burden have been made decades after incorporation of vastly larger amounts of radium and mesothorium into the skeleton, with the result that estimation of the original body burden, and hence of the total dose to the bone, involves assumptions about the fraction excreted (Norris et al., 1955). Assessment of the relevant tumorigenic dose is further complicated by large variations in the macroscopic and microscopic distribution of radium within the skeleton, the dose to different areas of bone varying by an order of magnitude or more (Lamerton, 1960; Rowland, 1963).

5.29 Oncogenic effects of bone-seeking radionuclides other than radium have been documented thus far only in laboratory animals, and results of such studies are as yet fragmentary for species other than the mouse (see Andersen and Goldman, 1962; Casarett et al., 1962; Dougherty, 1962). In CF_1 mice, the oncogenic potency of various radioelements, as compared with radium per microcurie injected, has been tentatively estimated as follows: radium-226, 1.0; strontium-90, 0.2; strontium-89, 0.1; calcium-45, 0.05; and plutonium-239, 20 (Finkel, 1956). These comparative potency values may not be valid at low levels of oncogenic effect, however, because the dose-effect curves for the various nuclides are complex in shape and not parallel. Furthermore, since the values were based on comparison of the effects of the several nuclides in relation to the respective amounts of radioactivity injected rather than in relation to the respective doses of radiation to bone, they may not be applicable to animals that differ from mice in the geometry, growth, and metabolism of their bones (Finkel, 1958). It has been calculated for example, that the mouse skeleton absorbs only 32 percent of the available energy from strontium-90 plus yttrium-90 contained therein, whereas the larger skeleton of the dog absorbs 79 percent and that of man 88 percent (Parmley et al., 1962). On the basis of the mean dose to bone, plutonium-239 and radium-226 appear significantly more effective than strontium-90 in inducing osteosarcomas in dogs (Dougherty, 1964), but the data are preliminary and the basis for the differences remains to be determined; i.e., it is not clear to what extent the differences are attributable to the higher effectiveness of the alpha particles from plutonium-239 and radium-226, as compared with the beta particles from strontium-90 plus yttrium-90, or to what extent the differences are attributable to other factors, such as distribution of the radiation in bone.

5.30 The influence of time-intensity factors in the induction of bone tumors is uncertain (Finkel et al., 1964b; Lamerton, 1960; Lamerton, 1959). The relative tumorigenic effectiveness of multiple injections of a radionuclide, as compared with a single injection of

the same total dose, is difficult to evaluate because of differences in the distribution of the radioactivity within bone under the different conditions of administration. There is evidence, however, that irradiation at a low dose rate, through gradual incorporation of strontium-90 into the skeleton from the diet over a greatly protracted interval is substantially less oncogenic than irradiation at higher rates (Finkel et al., 1960).

5.31 The effects of physiological variables on susceptibility to induction of bone tumors are, likewise, poorly known. Strain and species variations in susceptibility among rodents are marked and unexplained (Lamerton, 1960; Law, 1960; Finkel et al., 1961). Age variations, similarly, have been noted in the carcinogenic response of animals to bone-seeking radionuclides, but it is not yet possible in such instances to determine the extent to which the observed variations may be ascribed to differences in uptake and retention of the nuclide and to what extent they reflect differences in radiosensitivity (Lamerton, 1960).

Tumors of the Thyroid

5.32 The relationship between irradiation and induction of thyroid tumors was evaluated in 1962 by a panel of the National Academy of Sciences-National Research Council (Federal Radiation Council Report *Pathological Effects of Thyroid Irradiation*, 1962). The conclusions reached at that time have been strengthened and extended by findings in the interim (Saenger et al., 1963; Lindsay and Chaikoff, 1964; Pifer and Hempelmann, 1964).

5.33 The situation at present may be summarized as follows: external radiation delivered to the thyroid at dose levels above 100 rads has been correlated with the appearance of thyroid nodules in human beings. In some studies, the incidence has appeared to be proportional to dose within the range of approximately 100 to 300 rads, from which the risk over this dose range has been estimated to be 1 per million person-years per rad during at least the first 16 years after exposure (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). It has been suggested that external radiation localized to the thyroid region alone (Pifer and Hempelmann, 1964) and radiation from radioactive iodine (Doniach, 1963) are less tumorigenic to the thyroid than is external radiation not so sharply localized. These studies imply that exposure of tissues other than the thyroid contributes indirectly to thyroid neoplasia or that the tumorigenic effect decreases with decreasing dose rate, or both; however, these questions remain open at present. The bulk of the thyroid tumors associated to date with radiation has occurred among people exposed to X-rays during childhood.

Other Neoplasms

5.34 Tumors of epithelial and fibro-vascular tissue adjoining cranial bone have been associated with irradiation from bone-seeking radionuclides in laboratory animals and human beings (e.g., Casarett et al., 1962; Hasterlik et al., 1964). Such tumors include squamous cell carcinomas of the paranasal sinuses, which are rare in the general population. Although the increased frequency of these neoplasms is attributable to radiation emanating from radioisotopes deposited in adjacent bone, quantitative dose-incidence data for such growths are lacking.

5.35 Tumors of tissues other than those mentioned in the foregoing paragraphs have been induced by irradiation, but the relative increase in their incidence appears to have been small in man. Therefore, although quantitative estimates are not possible, it is unlikely that the over-all risk of malignancy from whole body irradiation, as in the case of internally deposited cesium-137, will exceed by any large factor the risk of leukemia, thyroid tumors, and skeletal neoplasms (United Nations Scientific Committee on the Effects of Atomic Radiation, 1964). By the same token, the over-all risk of malignancy from exposure to internally deposited radioactive strontium is unlikely to exceed greatly the risk of skeletal tumors, leukemia, and cancers of soft tissue adjoining cranial bone.

Other Somatic Effects in Children and Adults

5.36 Although a number of permanent effects other than malignancy have been observed following postnatal exposure to radiation, few are of concern at low dose levels. One of these is nonspecific deterioration and life shortening from causes other than neoplasia. Data on animals indicate a dose-dependent shortening of life-span. Data on human beings (Seltser and Sartwell, 1964) are, likewise, consistent with a life-shortening effect of irradiation, but the relation to dose cannot be estimated from the limited information available at this time. It is clear that the effect is so small, however, as to be detectable only in sizeable populations and at dose levels exceeding 100 rads.

5.37 Effects on the growth and development of bone and teeth are well known (see Ellinger, 1957). Stunting effects are dose-dependent and vary inversely in relation to age and maturity. Effects of this sort have been reported in Japanese surviving exposure to A-bomb radiation in childhood (Greulich et al., 1953). Such effects have not been documented, however, at dose levels below 100 rads. Few data are available on their induction by administration of radionuclides, although impaired growth and deformation of bone have been noted in dogs with burdens of 300 microcuries of strontium-89 at birth and in mice under similar conditions(Finkel, 1947, and personal communication).

SUMMARY AND CONCLUSIONS

The possible biological effects of irradiation from internally deposited strontium-89, strontium-90, and cesium-137 have been reviewed. Particular consideration has been given to effects that might result from uptake of any one of these isotopes by a small fraction of the population over a short period of time under conditions leading to a cumulative average absorbed dose of the order of 25 rads or less to any tissue of the body within about one year after contamination.

Because of differences in the behavior of radioactive strontium and radioactive cesium in the body and differences in the radioactive decay rate of their several isotopes, the implications of internally deposited radioactive strontium differ from those of radioactive cesium. Cesium-137, a beta-emitter, is distributed relatively uniformly throughout soft tissues and gives rise to a gamma ray-emitting daughter element, resulting in irradiation of essentially the whole body. Strontium-89 and strontium-90, on the other hand, are localized chiefly in the skeleton and teeth and give rise to energetic beta-rays, which are considered to affect mainly the bone, bone marrow, and adjacent structures. Tissues remote from bone, such as the gonads, receive comparatively little irradiation from radioactive strontium, with the result that effects on these tissues are regarded as non-limiting under the conditions of interest in this report.

In the absence of direct observations of effects from internally deposited radioactive cesium and strontium in human beings, the evaluation has been based of necessity on extrapolation from the effects of these radionuclides in experimental animals and the effects of irradiation from other sources in man. The observed effects have resulted, however, from irradiation under conditions that do not precisely duplicate those associated with deposition of radioactive cesium and strontium in the human body under the hypothetical conditions of interest. Hence, the conclusions derived herein are considered tentative.

Risks of chief concern in the case of irradiation from internally deposited cesium-137 under the conditions in question are considered to be the following:

1. *Carcinogenic effects on the exposed embryo and fetus*

An association between cancer incidence in childhood and antenatal diagnostic X-ray examination has been reported, which implies that the frequency of cancer may be increased by a single exposure of the fetus to high dose-rate whole body radiation at dose levels of 5 rads or less (see paragraphs 5.6-5.12). If this interpretation is verified, similar carcinogenic effects on the fetus and embryo might result from 25 rads delivered over a period of weeks by cesium-137, but the degree to which the incidence of any such effect would be altered by the relatively low dose rates in question cannot be determined from the data now available. The reported association between prenatal exposure and cancer involves a dose of radiation smaller than that associated with any other comparable injury in man. It suggests that sensitivity to radiation carcinogenesis may be several times higher before birth than later in life. At present, therefore, the fetus is considered to represent the critical segment of the population for a given dose from cesium-137 under the conditions of interest in this report.

2. *Effects on the development of the exposed embryo and fetus*

Disturbances of growth have been noted in developing embryos of experimental animals after a single X-ray dose as low as 10-20 rads. Effects on the development of the human embryo and fetus might result, therefore, from comparable doses delivered by cesium-137, although it cannot be predicted from the evidence at hand what effects, if any, would occur at the low dose rates in question, particularly since the total dose received at any given stage in development would be small. The frequency and severity of any such effects would be expected to depend on the age of the embryo at the time of exposure.

3. *Carcinogenic effects on the exposed child and adult*

A dose-dependent increase in the incidence of leukemia, thyroid tumors, and, to a lesser extent, other neoplasms has been observed in man at dose levels of about 100 rads and more. The precise way in which the incidence of these effects is related to the dose and dose rate is not known, and it is not clear whether smaller amounts of radiation can augment the risk of cancer. The excess incidence of cancer demonstrably associated with high doses, however, is of the order of one additional neoplasm per million person-years at risk per rad, which can reasonably be assumed to represent an upper limit of any effect that might occur at lower doses and dose rates.

4. *Genetic effects*

It is assumed that any increase in radiation exposure to the germ cells causes some increase in the mutation rate. Hence, heritable effects may be expected to result from 25 rads under the conditions in question. However, 25 rads is below the limit of 50 rads for an individual recommended by the National Academy of Sciences-National Research Council Committee on Genetic Effects of Atomic Radiation in 1956. Furthermore, the radiation would presumably be received at dose rates lower than those which had to be considered by that Committee and would therefore be less damaging. Also, as long as the group exposed is small, the average dose to the population will not be greatly changed. Therefore, genetic considerations are not likely to be limiting if the exposed group constitutes a small fraction of the population.

Risks of chief concern in the case of irradiation from strontium-89 and strontium-90 under the conditions in question are considered to be the following:

1. *Carcinogenic effects on the exposed embryo and fetus*

The embryo does not take up radioactive strontium in its bone until the second trimester, when its osseous tissues begin to mineralize, but thereafter it incorporates the element throughout its skeleton. Indications that susceptibility to leukemogenesis by X-rays may be 2-5 times higher during the fetal period than in later life, and that fetal irradiation induces other neoplasms not known to be associated with irradiation in the adult (see paragraphs 5.6-5.12), imply that the probability of effects from a given concentration of radioactive strontium in bone may be maximal during prenatal development. On the other hand, retention of strontium may be limited by metabolic factors to a greater degree during the fetal period than later in life. Also irradiation from radiostrontium differs from X-irradiation in being concentrated in bone and bone marrow and in being absorbed during

an interval of months rather than seconds or minutes. The extent to which these differences may reduce the leukemogenic effectiveness of radioactive strontium, as compared with that of X-rays, is not known. Thus, whether exposure in utero to radiostrontium under the conditions of interest would increase the incidence of leukemia and other cancers in the exposed child cannot be decided conclusively from existing data. The inference that the fetus is the most critical member of the population must also be considered tentative.

2. *Disturbances of skeletal growth and development in the exposed embryo and fetus*

Since skeletal abnormalities have been noted in embryos of genetically susceptible laboratory animals after a single X-ray dose as low as 25 rads, it is conceivable that some human embryos might be affected by 25 rads delivered over a period of months from internally deposited strontium-89 or strontium-90. However, mouse embryos given approximately 12 rads daily for 15 days by continuous exposure to gamma rays showed no gross defects, presumably because the radiation was less effective at the lower dose rate. Thus, it is highly questionable that such effects would occur at a total dose of 25 rads under the low dose rates in question.

3. *Carcinogenic effects on the exposed child and adult*

Radioactive strontium has been observed to induce leukemia and bone tumors in dogs and swine, but few such animals have been studied to date, and the effects have not been demonstrated at average dose levels below about 900 rads. It is not clear whether strontium-89 or strontium-90 under the conditions of interest (i.e., 25 rads delivered over a period of months) would increase the incidence of these forms of cancer in man. Any increment above the natural incidence that might result under these circumstances would, however, be small.

REFERENCES

Aarkrog, A., Caesium-137 from fall-out in human milk. Nature *197*:667, 1962.

Ager, E. A., Schuman, L. M., Wallace, H. M., and Rosenfield, A. B., An epidemiologic study of childhood leukemia. Minnesota Med. Bull. *33*:253, 1962.

Andersen, A. C. and Goldman, M., Pathological sequelae in beagles following continuous feeding of Sr-90 at a toxic level, in *Some Aspects of Internal Irradiation,* pp. 319-328, ed. by T. F. Dougherty, W. S. S. Jee, C. W. Mays, and B. J. Stover, Pergamon Press, Oxford, 1962.

Andersen, A. C. and McKelvie, D. H., Pathology Report. 7th Annual Progress Report—*The Effects of Sr-90 and Ra-226 on the Beagle.* Radiobiology Project, School of Veterinary Medicine, Univ. of California, Davis. UCD 472-110, pp. 132-146, 1964.

Anderson, E. C., Schuch, R. L., Fisher, W. R., and Langham, W. H., Radioactivity of people and foods. Science *125*:1273, 157.

Anderson, R. E., Hoshino, T., and Yamamoto, T., Myelofibrosis with myeloid metaplasia in survivors of the atomic bomb in Hiroshima. Annals of Internal Med. *60*:1-18, 1964.

Anderson, R. E. and Ishida, K., Malignant lymphoma in survivors of the atomic bomb in Hiroshima. Annals of Internal Med. *61*:5, 853-862, 1964.

Bengtason, L. G., Naversten, J., and Svensson, K. G., Maternal and infantile metabolism of cesium, in Symposium on *Assessment of Radioactive Body Burdens in Man,* Heidelburg, May 11-16, 1964. IAEA Vienna, SM/52-51.

Benison, D., Ramos, E., and Touzet, R., Strontium-90 levels in the diets and bones of children, USAEC Health and Safety Laboratory, Vol. 149, October 1964.

Binhammer, R. T., Finerty, J. C., Schneider, M., and Cunningham, A. W. B., Tumor induction in rats by single total-body X-irradiation, Radiation Research *6*:339-348, 1957.

Biskis, B. O., Finkel, M. P., and Greco, I. L., Myelogenous leukemia and acute reticulosis in beagles after Sr-90 administration, Radiation Research *22*:169, 1964.

Bloch, C., Postradiation osteogenic sarcoma, Am. J. Roentgenol. Radium Therapy and Nuclear Med. *87*(6):1157-1162, 1962.

Bryant, F. J. and Loutit, J. F., The entry of strontium-90 into human bone, Proc. Royal Soc., Series B, *159*:449-465, 1964.

Bureau of the Census and Div. of Radiol. Health, P. H. S., Consumption of selected food items in U. S. households, Radiological Health Data, *4*:3, 124-129, March 1963.

Burrow, G. N., Hamilton, H. B., Hrubec, Z., Amamoto, K., Matsunaga, F., and Brill, A. B., Study of adolescents exposed in utero to the atomic bomb, Nagasaki, Japan. I. General aspects: clinical and laboratory data, The Yale Journal of Biology and Medicine, *36*(6): 430-444, 1964.

Caldecott, R. S. and Snyder, L. A., eds., *Radioisotopes in the Biosphere*, Univ. of Minnesota, Minneapolis, 1960.

Casarett, L. W. T. and Baxter, R. C., Pathology of imbibed Sr-90 in rats and monkeys. Some aspects of internal irradiation, pp. 329-339, ed. by T. F. Dougherty, W. S. S. Jee, C. W. Mays, and B. J. Stover, Pergamon Press, Oxford, 1962.

Cater, D. B., Baserga, R., and Lisco, H., Studies on the induction of bone and soft tissue tumors in rats by gamma irradiation and the effect of growth hormone and thyroxine, Brit. J. Cancer *13*:214-227, 1959.

Cheeseman, E. A. and Walby, A. L., Intra-uterine irradiation and iris heterochromia, Ann. Hum. Genet., London, *27*:23, 1963.

Cohn, S. H., Spencer, H., Samachson, J., and Robertson, J. S., The turnover of strontium-85 in man as determined by whole-body counting, Radiation Research *17*:173-185, 1962.

Comar, C. L., Kostial, K., Grunden, N., and Harrison, G. E., *Metabolism of Strontium in the Newborn*, in preparation.

Comar, C. L. and Wasserman, R. H., *Strontium*, in *Mineral Metabolism*, Vol. 2, part A, pp. 523-572, ed. by C. L. Comar and F. Bonner, Academic Press, New York, 1964.

Court-Brown, W. M. and Doll, R., Adult leukemia trends in mortality in relation to etiology, Brit. Med. J. *1*:1063, 1959.

Court-Brown, W. M., Doll, R., and Hill, A. B., Incidence of leukemia after exposure to diagnostic radiation in utero, Brit. Med. J. *2*:1539, 1960.

Decker, C. F., Kaspar, L. V., and Norris, W. P., The variation of strontium metabolism with age in the dog. Radiation Research *23*:475-490, 1964.

Doniach, I., Effects including carcinogenesis of I-131 and X-rays on the thyroid of experimental animals: a review. Health Physics *9*:1357-1362, 1963.

Dougherty, T. F., Study of the long term biological effects of internal irradiation in adult beagles, in *Some Aspects of Internal Irradiation*, pp. 3-6, ed. by T. F. Dougherty, W. S. S. Jee, C. W. Mays, and B. J. Stover, Pergamon Press, Oxford, 1962.

Dougherty, T. F. (ed) Injection Tables. Research in Radiobiology. Radiobiology Div., Dept. of Anatomy, Univ. of Utah College of Med., C00-119-229, pp. 2-57, 1964.

Ehling, U. H., Frequency of X-ray induced presumed dominant mutations affecting the skeleton of mice. Genetics *50*:246, 1964.

Ehling, U. H. and Randolph, M. L., Skeletal abnormalities in the F_1 generation of mice exposed to ionizing radiations. Genetics *47*:1543-1555, 1962.

Ellinger, F., *Medical Radiation Biology*. Charles C. Thomas, Springfield, 1957.

Federal Radiation Council, *Health Implications of Fallout from Nuclear Weapons Testing through 1961.* Report No. 3, May 1962, U. S. Government Printing Office, Washington, D. C.

Federal Radiation Council, *Pathological Effects of Thyroid Irradiation* (A Report of a Panel of Experts from the Committees on the Biological Effects of Atomic Radiation: National Academy of Sciences-National Research Council), July 1962.

Federal Radiation Council, *Background Material for the Development of Radiation Protection Standards.* Report No. 5, July 1964, U. S. Government Printing Office, Washington, D. C.

Finkel, M. P., The transmission of radiostrontium and plutonium from mother to offspring in laboratory animals. Physiol. Zool. *20*:405-421, 1947.

Finkel, M. P., Relative biological effectiveness of internal emitters. Radiology *67*:665-672, 1956.

Finkel, M. P., Mice, men, and fallout. Science *128*:637-641, 1958.

Finkel, M. P., Late effects of internally deposited radioisotopes in laboratory animals. Radiation Research, Suppl. 1, 265-279, 1959.

Finkel, M. P., Bergstrand, P. J., and Biskis, B. O., The consequences of the continuous ingestion of Sr-90 by mice. Radiology *74*:458-467, 1960.

Finkel, M. P., Bergstrand, P. J., and Biskis, B. O., The latent period, incidence, and growth of Sr-90-induced osteosarcomas in CF_1 and CBA mice. Radiology *77*:269-281, 1961.

Finkel, M. P., Bergstrand, P. J., and Graubard, D. J., The uptake and retention of dietary strontium-90. Argonne National Laboratory Report ANL-6368, pp. 71-77, 1960.

Finkel, M. P., Biskis, B. O., and Jinkins, P. B., Neoplasms in mice produced by partial-body exposure to X-rays. Radiation Research *22*:188, 1964a.

Finkel, M. P., Jinkins, P. B., and Biskis, B. O., Parameters of radiation dosage that influence production of osteogenic sarcomas in mice, in *International Symposium on the Control of Cell Division and the Induction of Cancer,* pp. 243-270, ed. by C. C. Congdon and P. Mori-Chavez, National Cancer Institute Monograph *14*:1964b.

Folley, H. H., Borges, W. H., and Yamawaki, T., Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki. Am. J. Med. *13*:311, 1952.

Food and Nutrition Board, National Academy of Sciences-National Research Council, Report, *Recommended Dietary Allowances.* Publication 589, 1958 and 1963 revision.

Ford, D. D., Paterson, J. C. S., and Treuting, W. L., Fetal exposure to diagnostic X-rays and leukemia and other malignant diseases in childhood. J. Natl. Cancer Institute *22*:1093, 1959.

Gran, F. C. and Nicolaysen, R., Radio-strontium deposition in humans. Acta Physiol. Scan. *61*:Suppl. 223, 1964.

Greulich, W. W., Crismon, C. S., and Turner, M. L., Physical growth and development of children who survived bombing of Hiroshima or Nagasaki. J. Pediat. 43:121-145, 1953.

Halnan, K. E. and Pochin, E. E., The use of iodine-132 for thyroid function tests. Brit. J. Radiol. *31*:581-588, 1958.

Hammond, S. E., Bold, F. O., and MacDonald, N. S., Cesium-137 excretion and retention following single exposure. Health Physics *9*:523, 1963.

Hanson, W. C., Palmer, H. E., and Griffin, B. I., Radioactivity in Northern Alaskan Eskimos and their foods, Summer 1962. Health Physics *10*:421, 1964.

Hasterlik, R. J., Finkel, A. J., and Miller, C. E., The cancer hazards of industrial and accidental exposure to radioactive isotopes, in *Unusual Forms and Aspects of Cancer in Man*, pp. 832-837, ed. by H. E. Whipple and N. H. Moss, Annals N. Y. Acad. Sci. *114*:1964.

Henricson, B. and Nilsson, A., Chromosome investigations on the embryo progeny of male mice treated with ^{90}Sr. Acta Radiol. (n.s. Ther., Phys., Biol.) *2*:315-320, 1964.

Hicks, S. P. and D'Amato, C. J., Low dose radiation on developing brain. Science *141*:903-905, 1963.

Hood, S. L. and Comar, C. L., Metabolism of cesium-137 in rats and farm animals. Arch. Biochem. Biophys. *25*:423, 1953.

International Commission on Radiological Protection, Recommendations of, Report of Committee II on permissible dose for internal radiation. Health Physics *3*:1-380, 1960.

International Commission on Radiological Protection, Recommendations of, ICRP Publication 6, Pergamon Press, Oxford, 1964. (Radiation Protection)

Jones, A., Irradiation sarcoma. Brit. J. Radiol. *26*:273-284, 1953.

Kaplan, H. S., An evaluation of the somatic and genetic hazards of the medical uses of radiation. Am. J. Roentgenology *80*:696, 1958.

Kjeldsberg, H., Relation between leukemia and X-rays. Tidsskr. norske laegerfor. *77*:1052, 1957.

Koletsky, S. and Gustafson, G. E., Whole-body radiation as a carcinogenic agent. Cancer Research *15*:100-104, 1955.

La Croix, P. and Budy, A. M., *Radioisotopes and Bone.* Blackwell Scientific Publications, Oxford, 1962.

Lamerton, L. F., Dosimetry aspects of the production of bone tumours by radiation. Progress in Nuclear Energy, Series VII, Vol. 2, Medical Sciences, Pergamon Press, London, pp. 9-20, 1959.

Lamerton, L. F., Radioisotopes in the skeleton: Consideration of radiation dosage in relation to bone damage. *Radioisotopes in the Biosphere*, pp. 382-400, ed. by R. S. Caldecott and L. A. Snyder, Center for Continuation Study, Univ. Minnesota, Minneapolis, 1960.

Law, L. W., Radiation Carcinogenesis, in *Advances in Biological and Medical Physics*, Vol. VII, Academic Press, pp. 295-342, 1960.

Lejeune, J., Turpin, R., Rethoré, M.-O., and Mayer, M., Résultats d'une première enquête sur les effets somatiques de l'irradiation foetoembryonnaire in utero (cas particulier de hétérochromies iriennes). Rev. Franc. Etudes Clin. et Biol. *5*:982, 1960.

Lewis, E. B., Leukemia, multiple myeloma, and aplastic anemia in American radiologists. Science *142*:1492-1494, 1963.

Lewis, T. L. T., Leukemia in childhood after antenatal exposure to X-rays. Brit. Med. J. *2*:1551, 1960.

Liden, K., Cesium-137 burdens in Swedish Laplanders and reindeer. Acta Radiol. *56*:237, 1962.

Lindsay, S. and Chaikoff, I. L., The effects of irradiation on the thyroid gland with particular reference to the induction of thyroid neoplasms: A review. Cancer Research *24*:1099-1107, 1964.

Loevinger, R., Holt, J. G., and Hine, G. J., Internally administered radioisotopes, in *Radiation Dosimetry*, pp. 803-873, ed. by G. J. Hine and G. L. Brownell, Academic Press, New York, 1956.

Lough, S. A., Rivera, J., and Comar, C. L., Retention of strontium, calcium, and phosphorus in human infants. Proc. Soc. Exptl. Biol. Med. *112*:631-636, 1963.

Loutit, J. F., *Irradiation of Mice and Men.* University of Chicago Press, Chicago, 1962.

Lüning, K. G., Frölen, H., Nelson, A., and Rönnbäck, C., Genetic effects of strontium-90 injected into male mice. Nature *197*:304-305, 1963a.

Lüning, K. G., Frölen, H., Nelson, A., and Rönnbäck, C., Genetic effects of strontium-90 on immature germ-cells in mice. Nature *199*:303-304, 1963b.

MacMahon, B., Prenatal X-ray exposure and childhood cancer. J. Natl. Cancer Inst. *28*: 1173, 1962.

MacMahon, B. and Hutchison, G. B., Prenatal X-ray and childhood cancer: A review. Acta Unio Internat. Contra Cancrum, in press, 1964. (See: Hearings, Subcommittee on Research, Development, and Radiation, JCAE, 88th Congress, August 20-27, 1963, Part 2, p. 597.)

Marinelli, L. D., Radioactivity and the human skeleton. Janeway Lecture, 1958. Am. J. Roentgenol., Radium Therapy and Nuclear Med. *80*:729-739, 1958.

Mays, C. W., Stover, B. J., Glad, B. W., and Atherton, D. R., Skeletal dosimetry in Utah beagles, Annual Prog. Rep. Radiogiol. Lab. Univ. of Utah, C00-218, pp. 121-139, 1959.

McClellan, R. O. and Bustad, L. K., Toxicity of significant radionuclides in large animals. Ann. N. Y. Acad. Sci. *3*:793-811, 1964.

Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations.* Her Majesty's Stationery Office, London, 1956.

Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations. A Second Report to the Medical Research Council.* Her Majesty's Stationery Office, London, 1960.

Mitchell, H. H., Hamilton, T. S., Steggerda, F. R., and Bean, H. W., The chemical composition of the adult human body and its bearing on the biochemistry of growth. J. Biol. Chem. *158*:625-637, 1945.

Moffett, R. E., Lundquist, L., and Johnson, S., *The school milk program.* Bull. 368, Univ. Connecticut, Nov. 1961.

Mole, R. H., Induction by radiation of leukemias and other malignant diseases of haematopoietic cells in experimental animals. Bull. WHO Geneva *26*:613-618, 1962.

Moloney, W. C., Induction of leukemia in man by radiation. *Symposium on Radiation Biology and Cancer.* M. D. Anderson Hospital, Houston, Texas, University of Texas Press, Austin, p. 344, 1959.

Moore, W., Jr. and Comar, C. L., Foetal metabolism of caesium-137. Intern. J. Rad. Biol. *6*:233, 1963.

Murray, R., Heckel, P., and Hempelmann, L. H., Leukemia in children exposed to ionizing radiation. New Engl. J. Med. *261*:585, 1959.

National Academy of Sciences-National Research Council, *The Biological Effects of Atomic Radiation, Summary Reports.* NAS-NRC, Washington, 1956.

National Academy of Sciences-National Research Council, *The Biological Effects of Atomic Radiation, Summary Reports.* NAS-NRC, Washington, 1960.

Newcombe, H. B. and McGregor, J. F., Learning ability and physical well-being in offspring from rat populations irradiated over many generations. Genetics *50*(Part 2):1065-1081, 1964.

Nold, M. M., Tapper, D. N., and Comar, C. L., Cs-137 dose measurements in tissue—II. Health Physics *8*:217, 1962.

Norman, A., Sasaki, M., Ottoman, R. E., and Veomett, R. C., Chromosome aberrations in radiation workers. Radiation Research *23*:282-289, 1964.

Norris, W. P., Speckman, T. W., and Gustafson, P. F., Studies of the metabolism of radium in man. Am. J. Roentgenol. *73*:785-802, 1955.

Osgood, E. E., Contrasting incidence of acute monocytic and granulocytic leukemias in P-32 treated patients with polycythemia vera and chronic lymphocytic leukemia. J. Lab. & Clin. Med. *64*:560-573, 1964.

Parmley, W. W., Jensen, J. B., and Mays, C. W., Skeletal self-absorption of beta-particle energy, in *Some Aspects of Internal Irradiation,* ed. by T. F. Dougherty, W. S. S. Jee, C. W. Mays, and B. J. Stover, Pergamon Press, New York, pp. 437-451, 1962.

Pifer, J. W. and Hempelmann, L. H., Radiation-induced thyroid carcinoma, in *Unusual Forms and Aspects of Cancer in Man.* Annals N. Y. Acad. Sci. 114(Art. 2):838-848, 1964.

Pifer, J. W., Toyooka, E. T., Murray, R. W., Ames, W. R., and Hempelmann, L. H., Neoplasms in children treated with X-rays for thymic enlargement. I Neoplasms and mortality. J. Natl. Cancer Inst. *31*:1333-1356, 1963.

Piontkovsky, I. A., Effects of ionizing radiation on the function of higher nervous system of progeny. Medgiz, Moscow, 1961. U. S. Atomic Energy Commission, Translation Series, AEC-tr-5553.

Piontkovsky, I. A. and Semagin, V. N., Some peculiarities of the higher nervous activity of adult animals subjected antenatally to ionizing irradiation. Report IV. The state of the higher nervous activity in adult albino rats daily irradiated with a low X-ray dose during the whole period of antenatal development. Bull. Exper. Biol. & Med. *11*:18-22, 1961 (English summary).

Polhemus, D. W. and Koch, R., Leukemia and medical radiation. Pediatrics *23*:453, 1959.

Roderick, T. H., ed. *The Effects of Radiation on the Hereditary Fitness of Mammalian Populations.* Proceedings of Symposium held at the Jackson Laboratory, Bar Harbor, Maine, June 29-30 and July 1, 1964. Genetics *50*(Part 2):1019-1217, 1964.

Rowland, R. E., Some aspects of human bone metabolism deduced from studies of radium cases. Clinical Orthopaedics *28*:193-203, 1963.

Russell, L. B., Effects of low doses of X-rays on embronic development in the mouse. Proc. Soc. Exptl. Biol. Med. *95*:174-178, 1957.

Russell, L. B., Badgett, S. K., and Saylors, C. L., Comparison of the effects of acute, continuous, and fractionated irradiation during embryonic development, in *Immediate and Low Level Effects of Ionizing Radiation.* Suppl. International J. Rad. Biol., pp. 343-359, 1960.

Russell, W. L., The effect of radiation dose rate and fractionation on mutation in mice, in *Repair from Genetic Radiation Damage*, ed. by F. H. Sobels, Pergamon Press, Oxford, pp. 205-217, 1963.

Saenger, E. L., Seltzer, R. A., Sterling, T. D., and Kereiakes, J. G., Carcinogenic effects of I-131 compared with X-irradiation: A review. Health Physics *9*:1371-1384, 1963.

Seltser, R. and Sartwell, P. B., The effect of occupational exposure to radiation on the mortality of physicians. JAMA *190*:1046-1048, 1964.

Sinclair, W. K., in *Proc. Conf. of Radioiodine.* Nov. 5-6, 1956, Argonne Cancer Research Hospital, Chicago, University of Chicago Press, p. 9, 1957.

Speckman, T. W. and Norris, W. P., The age-dependence of strontium retention in rats and mice. Radiation Research *23*:461-474, 1964.

Stewart, A., Webb, J., Giles, D., and Hewitt, D., Malignant disease in childhood and diagnostic irradiation *in utero:* preliminary communication. Lancet *2*:447, 1956.

Stewart, A., Webb, J., and Hewitt, D., A survey of childhood malignancies. Brit. Med. J. *1*:1495, 1958.

Stewart, C. G., Vogt, E., Hitchman, A. J. W., and Jupe, M., The excretion of strontium-90 and caesium-137 by the human. *Proceedings Second Conference on Peaceful Uses of Atomic Energy*, Vol. 23, p. 123, United Nations, Geneva, 1958.

Toyooka, E. T., Pifer, J. W., Crump, S. L., Dutton, A. M., and Hempelmann, L. H., Neoplasms in children treated with X-rays for thymic enlargement. II. Tumor incidence as a function of radiation factors. J. Natl. Cancer Inst. *31*:1375-1377, 1963.

United Nations Scientific Committee on the Effects of Atomic Radiation, Report of, United Nations, Seventeenth Session, Suppl. No. 16 (A/5216). New York, 1962.

United Nations Scientific Committee on the Effects of Atomic Radiation, Report of, United Nations, Nineteenth Session, Suppl. No. 14 (A/5814). New York, 1964.

Upton, A. C., Comparative aspects of carcinogenesis by ionizing radiation. National Cancer Inst. Monograph *14*:221-239, 1964.

Wasserman, R. H., ed. *The Transfer of Calcium and Strontium Across Biological Membranes.* Academic Press, New York, 1963.

Watanabe, S., Experimental studies on the development of leukemia in mice with frequent administrations of small doses of some radioactive isotopes (P-32, Sr-89, Ce-144), Gakujutsu Geppo (Japanese Scientific Monthly) *10*:5, Nov. 1957.

Wells, J. and Steer, C. M., Relationship of leukemia in children to abdominal irradiation. Am. J. Ob. Gyn. *81*:1059, 1961.

Yamagata, N., Estimation of the total-body load of Caesium-137 in Japanese people. Nature *196*:284, 1962.

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